## DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338 Expiration Date: Merch 31, 2003 See OMB Statement on page 2.

APPLICATION NUMBER

# APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

FOR FDA USE ONLY

(Title 21, Code of Federal Regulations, 314 & 601) APPLICANT INFORMATION DATE OF SUBMISSION NAME OF APPLICANT FACSIMILE (FAX) Number (Include Area Code) The R.W. Johnson Pharmaceutical Research Institute TELEPHONE NO. (Include Area Code) (908) 203-1499 (908) 704-4812 APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE 920 Route 202 South P.O. Box 300 Raritan, New Jersey 08869-0602 PRODUCT DESCRIPTION NDA 21-180 NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously leaved) PROPRIETARY NAME (trade name) IF ANY ESTABLISHED NAME (e.g., Proper name, USP/USAN name) norelgestromin and ethinyl estradici ORTHO EVRAM CODE NAME (If any) CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) ROUTE OF ADMINISTRATION: DOSAGE FORM: STRENGTH8: Transdormai 150 mcg norelgestromin transdermal patch 20 mcg ethinyl estradiol (PROPOSED) INDICATION(6) FOR USE: Prevention of Pregnancy **PPLICATION INFORMATION** JPPLICATION TYPE MEW DRUG APPLICATION (21 CFR 314.50) (check one) BIOLOGICS LICENSE APPLICATION (21 CFR part 601) IF AN NDA, IDENTIFY THE APPROPRIATE TYPE (1) 505 (b) (1) S05 (b) (2) IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Holder of Approved Application Name of Drug MENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION TYPE OF SUBMISSION (check one) ORIGINAL APPLICATION PRESUBMISSION ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT TO EFFICACY SUPPLEMENT II LABELING SUPPLEMENT CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE C8E-30 Prior Approval (PA) RESPONSE TO FDA REQUEST TO PROVIDE ADDITIONAL FINANCIAL DISCLOSURE INFORMATION REASON FOR SUBMISSION PRESCRIPTION PRODUCT (Rx) PROPOSED MARKETING STATUS (check one) OVER THE COUNTER PRODUCT (OTC) THIS APPLICATION IS ☐ PAPER PAPER AND ELECTRONIC | ELECTRONIC NUMBER OF VOLUMES SUBMITTED ESTABLISHMENT INFORMATION (Full establishment should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contect, telephone number, registration number (CFN). DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability teating) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready. Cross References (flat related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

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ľ	m [	1. Index			
Ī	×	2. Labeling (check one)	□ Draft Labeling	☐ Finel Printed	Labeling
Ţ		3. Summary (21 CFR 314.50 (c	:))		
	7	4. Chemistry section			
Ì		A. Chemistry, manufacturin	g, and controls information (e.g. 21 CFR 314.50 (c	i) (1), 21 CFR 601.2)	
Ì	$\overline{\Box}$		0 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FD		•
Ì			age (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)		
Ì			nd toxicology section (e.g. 21 CFR 314.50 (d) (2),		
ľ			d bioavallability section (e.g. 21 CFR 314.50 (d) (		
I		7. Clinical Microbiology (e.g. 21	<del>***</del>		
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١	<u> </u>		CFR 314.50 (d) (5), 21 CFR 601.2)		
I			CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)	<u> </u>	
1			FR 314.50 (d) (6), 21 CFR 601.2)	•	
I			21 CFR 314.50 (f) (1), 21 CFR 601.2)		<del></del>
1		12. Case reports forms (e.g. 21	CFR 314.50 (f) (2), 21 CFR 601.2)	; 	
1		13. Patent information on any pa	atent which claims the drug (21 U.S.C 355 (b) or (c	<del>))</del>	·
	Д_	14. A patent certification with res	spect to any patent which claims the drug (21 U.S.	C 355 (b) (2) or (j) (2) (A))	
		15. Establishment description (2	1 CFR Part 600, If applicable)		į.
•		16. Debarment certification (FDI	SC Act 306 (k) (1))		
:	П	17. Field copy certification (21 C	FR.314.50 (k) (3))		
:		18. User Fee Cover Sheet (Form	n FDA 3397)		
ı		19. Financial information (21 CF	R Part 64)		
		20. OTHER (Specify)		· · · · · · · · · · · · · · · · · · ·	
:		CATION			
			safety information about the product that may rea ns in the draft labeling. I agree to submit safety up		
	request	ed by FDA. If this application is ap	proved, I agree to comply with all applicable laws		
1	i	g, but not limited to the following: Good manufacturing practice recu	lations in 21 CFR 210 and 211, 606 and/or 820.		
:		Biological establishment standard			
	3.	Labeling regulations in 21 CFR 20	11, 606, 610, 660 and/or 809.		
		, - , -	or biological product, prescription drug advertising	- ;	
	1		n <b>application</b> in 21 CFR 314.70, 314.71, 314.72, 31	14.97, 314.99, and 601.12.	
		Local, state and Federal environm	314.80, 314.81, 600.80 and 600.81.		•
			t that FDA has proposed for scheduling under the	Controlled Substances Act 1:	acree not to market the
	product	until the Drug Enforcement Admir	distration makes a final scheduling decision.		-
			on have been reviewed and, to the best of my known infinial offense, U.S. Code, title 18, section 1001.	Medge are certified to be true	and accurate.
	_	URE OFFICIAL			DATE
		V Alain A Dome	Ramon Polo, PhD	Affalas	1 6 NOV 2001
	ADDRE	SS (Street, City, State, and ZIP (God	Director, Regulatory	Attairs Telephone Number	
:		920 Route 202 South, P.O.	Box 300 '	(908) 704-4812	•
	Omblic	Raritan, New Jersey 08869		40 have	
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Public reporting burden for this collection of information is estimated to everage 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

artment of Health and Human Services
Local and Drug Administration
CBER, HFM-99
1401 Rockville Piles
Rockville, MD 20852-1448
FORM FBA 3561/406)

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

1/4/14

# THE R.W. JOHNSON PHARMACEUTICAL RESEARCH INSTITUTE

920 U.S. Route # 202, P.O. Box 300 Raritan, New Jersey 08869-602

### TELEFACSIMILE TRANSMITTAL FORM

FAX NUMBER: (908) 203-1499

DATE:

16 November 2001

TO:

JENNIFER MERCIER

Project Manager, FDA

Div. Reprod. & Urol. Drug Products

FROM: Valerie Donnelly

Regulatory Affairs Phone: (908) 704-5891 Fax: (908) 203-1499

TELEFAX #:

(301) 827-4267

NUMBER OF PAGES (INCLUDING TRANSMITTAL FORM): 5

NOTE: If you do not receive the correct number of pages or if the transmission is unclear, please call me at (908) 704-5891.

#### MESSAGE (If any):

JENNIFER,

RE: NDA 21-180 ORTHO EVRA™ dissolution specifications

ATTACHED IS A FAXED VERSION OF OUR RESPONSE TO FDA'S REQUEST THAT WE REVISE THE DISSOLUTION SPECS. A hard copy submission will follow tomorrow morning. f you have additional questions or comments on this submission, please call me at (908) 704-5891. THANKYOU

#### CONFIDENTIALITY NOTICE

This facsimile transmission cover sheet and any documents which may accompany it contains information from Johnson & Johnson, which is intended only for the use of the individual or entity to which it is addressed and which may contain information that is privileged, confidential, and/or exempt from disclosure under applicable law. If the reader of this message is not the intended recipient, any disclosure dissemination, distribution, copying, or other use of this communication or its substance is prohibited. If you have received this communication in error, please call us collect to arrange for the destruction of the communication or its return to us at our expense. Thank you.



# THE R.W. JOHNSON PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08809-0602

Faxed NOV 16,01

Dr. Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug
Product

Attn.: Document Control Room 14B-04 5600 Fishers Lane Rockville, Maryland 20857-1706 NDA 21-180
ORTHO EVRATM
(norelgestromin/ethinyl estradiol transdermal system)

Amendment to a Pending
Application:
Response to FDA Request For
CM&C Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180 for Oli THO EVRATM, a norelgestromin (NGMN) and ethinyl estradiol (EE) transdermal contraceptive system, submitted on 20 December 2000. Reference is also made to the 15 November 2001 teleconference with the Division to discuss the dissolution specifications for the drug product. FDA's requested RWJPRI to revise the specifications submitted in the NDA to the new specifications calculated by FDA.

Old NDA New Interim FDA calculated

Test Attribute Specification Specification

Drug Release
a) Norelgestromin (NGMN)

b) Ethinyl estradiol (EE)

RWJPRI agrees to accept the interim specifications above, as calculated by FDA. We will re-test the lots in stock according to the new specifications calculated by FDA. We also agree with the proposal to come back to the Agency as soon as we have additional data on production batches and a justification for setting new specifications.

WARLISBARESO WEITSBECKCYCRUS/LTR/11601 response to 6th req CMC info.doc/16 November 2001/8/1/3

LA JOLLA

RARITAN

SPRING HOUSE

ZURICI

Should you have any questions and/or comments, please contact me at (908) 704,4812, contact Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

The R.W. Johnson Pharmaceutical Research Institute

Ramon Polo, PhD

Director

Regulatory Affairs

Send deak copies to:

Dr. Mhoojong Rhee - FDA/DRUDP/HFD-580, Chem-pharm Team Leader

Dr. Amit Mitra - FDA/DRUDP/HFD-580, Chemistry Reviewer

Dr. Dhruba Chatterjee - FDA/DRUDP/HFD-580, Biopharm Reviewer

APPEARS THIS WAY

PAGE 1

### **DEPARTMENT OF HEALTH AND HUMAN SERVICES**

FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN

**ANTIBIOTIC DRUG FOR HUMAN USE** (Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-033& Expiration Date: March 31, 2003 See OMB Statement on page 2.

FOR FOA USE ONLY

APPLICATION NUMBER

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APPLICANT INFORMATION			·		
NAME OF APPLICANT The R.W. Johnson Pharmaceutical Research Institute  DATE OF SUBMISSION					
TELEPHONE NO. (Include Area Code)		FACSIMILE (F	AX) Number (Include Area Code)	15	
(908) 704-4812			203-1499	ŗ	
APPLICANT ADDRESS (Number, Street, City, Strend U.S. License number if previously issued): 920 Route 202 South P.O. Box 300 Raritan, New Jersey 08869-060			S. AGENT NAME & ADDRESS (Number, Sone & FAX number) IF APPLICABLE	ore, City, State,	
PRODUCT DESCRIPTION					
NEW DRUG OR ANTIBIOTIC APPLICATION NUI	MBER, OR BIOLOGICS LICENSE A	PPLICATION NUMBER	(If proviously issued) NDA 21-180		
ESTABLISHED NAME (e.g., Proper name, USPA norelgestromin and ethinyl estradi		PROPRIETARY NAME ORTHO EVR		į.	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (# any)  CODE NAME (# any)					
DOSAGE FORM:  transdermal patch  6 mg norelgestromin  0.75 mg ethinyl estradiol					
(PROPOSED) INDICATION(S) FOR USE: Prevention of Pregnancy					
APPLICATION INFORMATION					
(check one) NEW DRUG APPLICAT	TION (21 CFR 314.50) ABBR		N (ANDA, AADA, 21 CFR \$14,94)		
IF AN NOA, IDENTIFY THE APPROPRIATE TYP	E [] 505 (b) (1)	505 (b) (2)	· · · · · · · · · · · · · · · · · · ·	1:	
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TYPE OF SUBMISSION (check one)	PRIGINAL APPLICATION	MANENDMENT TO A PEN	IDING APPLICATION RESUBMIS	se <sup>‡</sup>	
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🖸 LABELING SUPPLEMENT 🔲 C	HEMISTRY MANUFACTURING AND CO	NTROLS SUPPLEMENT	☐ OTHER	1.	
IF A SUBMISSION OR PARTIAL APPLICATION,	PROVIDE LETTER DATE OF AGRE	EMENT TO PARTIAL S	UBMISSION:		
IF A SUPPLEMENT, IDENTIFY THE APPROPRI			Prior Approval (PA)		
REASON FOR SUBMISSION RESPONSE TO	FDA REQUEST FOR CMAC INFOR			i c	
PROPOSED MARKETING STATUS (check one)	PRESCRIPTION PRODUCT (	Rx) 🗀 OV	ER THE COUNTER PRODUCT (OTC)		
NUMBER OF VOLUMES SUBMITTED	THIS APPLICATION I		<u> </u>	ELE TRONIC	
ESTABLISHMENT INFORMATION (Full establish Provide locations of all manufacturing, packaging contact, talephone number, registration number (Caite. Please indicate whether the site is ready for I	and control sites for drug substance : CFN), DMF number, and manufacturit	and drug product (continu	uation sheets may be used if necessary) for	dude Name, address, g) conducted at the	
Gross References (list related License Applica	dons, INDs, NDAs, PMAs, 510(k)s,	IDEs, BMFs, and DMFs	referenced in the current application)		
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FORM FDA 366h (4/90)		· · · · · · · · · · · · · · · · · · ·		PAGE 1	

This ap	plication contains the following items: (Check all that apply)	······	<del>-</del>		
	1. Index		-		
	2. Labeling (check one) Draft Labeling	☐ Final Printed Labeling			
	3. Summery (21 CFR 314.50 (c))				
л_	4. Chemistry section		i		
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1	), 21 CFR 601.2)			
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's	request)			
	C. Methods velidation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)		<del></del>		
П	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 314.	OFR 601.2)			
	6. Human pharmacokinedos and bioavaitability section (e.g. 21 CFR 314.50 (d) (3), 2	11 CFR 601.2)	· · · · · · · · · · · · · · · · · · ·		
$\Box$	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))		:		
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)		-		
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vl) (b), 21 CFR 601.2)		<del></del>		
$\Box$	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)	Ţ	-		
$\Box$	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)		<del></del>		
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)				
	13. Patent information on any patent which claims the drug (21 U.S.C 355 (b) or (c))	EE 0-1 (0) 01 (0) (4))			
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 3	35 (D) (2) OF (J) (2) (A))			
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	17. Fleid copy certification (21 CFR 314.50 (k) (3))		<u> </u>		
Ц	18. User Fee Cover Sheet (Form FDA 3397)	·			
<u>'</u>	19. Financial Information (21 CFR Part 54)				
CEPTI	20. OTHER (Specify) Response to FDA Request for CM&C Information				
warning request includin	to update this application with new safety information about the product that may reason s, precautions, or adverse reactions in the draft labeling. I agree to submit safety update ed by FDA. If this application is approved, I agree to comply with all applicable laws and g, but not limited to the following:  Good manufacturing practice regulations in 21 CFR 210 and 211, 606 and/or 820.	reports as provided for by regulation	or all.		
	Biological establishment standards in 21 CFR Part 600.		<u>:</u>		
	Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.		<u>:</u>		
_	In the case of a prescription drug or biological product, prescription drug advantising regi		:		
5. 6.	Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.9 Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.	7, 314.99, and 601.12	į		
	Local, state and Federal environmental impact laws.		}		
If this a	pplication applies to a drug product that FDA has proposed for scheduling under the Con	strolled Substances Act I agree not to	market the		
product	until the Drug Enforcement Administration makes a final scheduling decision, a and information in this submission have been reviewed and, to the best of my knowled	las are cortified to be true and comm			
Warnin	g: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.	Arcel N			
SIGNAT	URE OF RESPONSIBLE OFFICIAL OR AGENT  TYPED NAME AND TITLE  ROMAN BOLD PLD	DATE			
	Ramon Polo, PhD Director, Regulatory Affi	airs	<u>.</u>		
ADDRE	SS (Street, City, State, and ZIP Code)	Telephone Number	<del></del> }		
	920 Route 202 South, P.O. Box 300  Raritan, New Jersey 08869-0602	(908) 704-4812	! !		

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time fir reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

apartment of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of Information unless it displays a currently valid OMB control number.



# THE R.W. JOHNSON PHARMACEUTICAL RESEARCH INSTITUTE 920 Route 202, P.O. Box 300 Raritan, NJ 08869-0602

### Fax Cover Sheet

Date:

November 16, 2001

Pages:

To:

Jennifer Mercier

From:

Karen Futterknecht

Dept.:

FDA

Dept.:

Regulatory Affairs

Fax #:

301-827-4267

Telephone #: 301-827-4249

Fax #:

908-722-5113

**Telephone #:** 908-704-4912

Comments:

# THE R.W. JOHNSON PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

14 MIN 2004

Susan Allen, MD, Director Division of Reproductive and Urologic Drug Products HFD-580

Center for Drug Evaluation and Research Food and Drug Administration Attn.: Document Control Room 14B-04

5600 Fishers Lane Rockville, Maryland 20857-1706 NDA 21-180
ORTHO EVRATM
(norelgestromin/ethinyl estradiol transdermal system)

AMENDMENT TO A
PENDING APPLICATION:
Labels/Labeling Information and

Dear Dr. Allen:

Reference is made to our pending NDA 21-180 for ORTHO EVRATM and to the draft package components submitted with the original application on 20 December 2000-NDA (Item 2, Item Volume 1, Pages 52-59). Reference is also made to the draft packaging components that were amended to the pending application on 05 October 2001. At this time we would like to amend the NDA to withdraw the component. Attached is a black and white copy of the component.

If you have questions regarding this information please contact me at (908)-704-4812 or Valerie Donnelly at (908)-704-5891 or our dedicated number for FDA use (908)-704-4600.

Sincerely,

The RW Johnson Pharmaceutical Research Institute

Ramon Polo Ph.D.

Director

Regulatory Affairs

Send 1 desk copy to: Dr. Amit Mitra, FDA/DRUDP/HFD-580, Reviewing Chemist Fax Copy to Jennifer Mercier

#### DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338 Expiration Date: Merch 31, 2003 See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

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APPLICANT INFORMATION						
NAME OF APPLICANT The R.W. Johnson Pharmaceutical Research Institute			OF SLIBMIS	SION	16 NOV	2001
TELEPHONE NO. (Include Area Gode)		1		Number (Include A	res Code)	
(908) 704-4812			(908) 203	<del></del>		
APPLICANT ADDRESS (Number, Street, City, St and U.S. License number if previously lesued):	ate, Country, ZIP Code or Mail Code,			GIENT NAME & AD A <i>FAX number</i> ) IF A		r, Street, City, State,
920 Route 202 South P.O. Box 300 Raritan, New Jersey 08869-060						
PRODUCT DESCRIPTION						
NEW DRUG OR ANTIBIOTIC APPLICATION NU	MBER, OR BIOLOGICS LICENSE A	PPLICATION NU	IMBER (If pr	eviously issued)	NDA 21-180	
ESTABLISHED NAME (e.g., Proper name, USP/ noreligestromin and ethinyl estrad	•		Y NAME (bac ) EVRATH	de name) IF ANY		
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT I	NAME (If eny)	<u> </u>		CODE NAME	(If any)	1.0.1
DOSAGE FORM: transdormal patch	STRENGTHS: 150 mcg noreigestrom 20 mcg ethinyl estrad		RO	Transderma		
(PROPOSED) INDICATION(8) FOR USE: Prevention of Prognancy						
PPLICATION INFORMATION		4	i			
	TION (21 CFR 914.50) [] ABBR	j,	CATION (A)	NDA, AADA, 21 CF	R 314.94)	
LI BIOLO	IGICS LICENSE APPLICATION (21	CFR part 601)		· .	·	
IF AN NOA IDENTIFY THE APPROPRIATE TYP		505 (b) (2)				
IF AN ANDA, OR AADA, IDENTIFY THE REFER Name of Drug	ENCE LISTED DRUG PRODUCT TH Holder of Approved		IS FOR THE	SUBMISSION		
TYPE OF SUBMISSION (check one)	ORIGINAL APPLICATION	B AMERICAERT	O A PENDING	APPLICATION	☐ RESUBA	IISSION
☐ PRESUBMISSION ☐ ANNUAL R	EPORT EST	ABLISHMENT DES	СРИРПОМ ВИ	PPLEMENT -	☐ EFFICACYS	UPPLEMENT
D LABELING SUPPLEMENT (2)	CHEMISTRY MANUFACTURING AND CO	NTROLS SUPPLEM	enti.	OTHER		
IF A SUBMISSION OR PARTIAL APPLICATION,	PROVIDE LETTER DATE OF AGRI	EEMENT TO PAF	RTIAĻ SUBM	ISSION:		
IF A SUPPLEMENT, IDENTIFY THE APPROPRI		☐ C8E-34	·	Prior Approval (PA)		
REASON FOR SUBMISSION RESPONSE TO	FDA REQUEST TO PROVIDE ADD	MITIONAL FINAN	CIAL DISCL	OSURE INFORMA	TION	
PROPOSED MARKETING STATUS (check one)	PRESCRIPTION PRODUCT	(Pbx)	□ OVER T	HE COUNTER PR	ODUCT (OTC)	
NUMBER OF VOLUMES SUBMITTED	THIS APPLICATION		<u> </u>	PAPER AND ELE	ECTRONIC E	ELECTRONIC
ESTABLISHMENT INFORMATION (Felt establishment of all manufacturing, packaging address, contact, telephone number, registration in conducted at the site. Please indicate whether the	and control sites for drug substance : number (CFN). DMF number, and me	and drug product	(continuation	n sheets may be us of testing (e.g. Fine	ed if riecessary). al dosage form. S	Include name. tability testing)
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Gross References (list related License Applica	mons, INDs, NDAs, PMAs, 610(k)s,	IDEs, BMFs, and	DMFs rete	renced in the curr	ent application)	
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This ap	plication contains the following items: (Check	all that apply)					
П	1. Index						
N	2. Labeling (check one)	□ Draft Labeling	Final Printed	Labeling			
X	3. Summary (21 CFR 314.50 (c))						
	4. Chemistry section						
	A. Chemistry, manufacturing, and controls in	formetion (e.g. 21 CER 314 50 (d) (1) 21	CER 601 2)				
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR			<del></del>			
	C. Methods validation package (e.g. 21 CFR		501)				
			204.0\				
	5. Nonclinical pharmacology and toxicology sed			<del></del>			
	6. Human pharmscokinetics and bioavallability s		-R 601.2)				
	8. Clinical data section (e.g. 21 CFR 314.50 (d)						
<u> </u>	9. Safety update report (e.g. 21 CFR 314.50 (d)	(5) (vi) (b), 21 CFR 801.2)		·			
Ю	10. Statistical section (e.g. 21 CFR 314.50 (d) (6)	, 21 CFR 601.2)					
	11. Case report tabulations (e.g. 21 CFR 314.50	(f) (1), 21 CFR 601.2)	<del></del>				
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2	r), 21 CFR 801.2)	· <del></del>				
	13. Patent Information on any patent which claims	s the drug (21 U.S.C 355 (b) or (c))	·· <del>·</del>				
	14. A patent certification with respect to any pate	nt which claims the drug (21 U.S.C 355 (b	) (2) or (1) (2) (A))				
	15. Establishment description (21 CFR Part 600,	if applicable)					
	16. Debarment certification (FD&C Act 308 (k) (1)	))					
	17. Field copy certification (21 CFR 314.50 (k) (3)	))					
	18. User Fee Cover Sheet (Form FDA 3397)						
<u></u>	19. Financial information (21 CFR Part 54)						
	20. OTHER (Specify)						
l agrae warning request includin	RCATION to update this application with new safety informations, precentions, or adverse reactions in the draft labored by FDA. If this application is approved, I agree to g, but not limited to the following:  Good manufacturing practice regulations in 21 CFF	aling. I agree to submit safety update repo comply with all applicable laws and regu	orts as provided for b	y regulation or as			
	Biological establishment standards in 21 CFR Part						
2	Labeling regulations in 21 CFR 201, 608, 610, 660		•	•			
4.	In the case of a preacription drug or biological prod	· · · · · · · · · · · · · · · · · · ·	· ·				
5.	Regulations on making changes in application in 21		4.99, and 601.12.				
	Regulations on reports in 21 CFR 314.80, 314.81, (Local, state and Federal environmental impact laws						
	pplication applies to a drug product that FDA has pr		ed Substances Act I a	agree not to market the			
product	until the Drug Enforcement Administration makes a a and information in this submission have been revi	I final scheduling decision.					
Warnin	g: a willfully false statement is a criminal offense, U	I.S. Code, title 18, section 1001.					
SIGNAT	URE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE		DATE 6 NOV 2001			
	Elin a Donnelly you	Ramon Polo, PhD Director, Regulatory Affairs					
ADDRE	SS (Street, City, State, and AP Code)		Telephone Number				
[·	920 Route 202 South, P.O. Box 300 Raritan, New Jersey 08889-0602		(908) 704-4812				
	The same state and same and	<del></del>	<del></del>				

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

artment of Health and Human Services .od and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448 An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.



# THE R.W. JOHNSON PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

faxed to FDA 13 NOV 2001 (UM)

Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug
Products

Attn.: Document Control Room 14B-04 5600 Fishers Lane Rockville, Maryland 20857-1706 NDA 21-180
ORTHO EVRATM
(norelgestromin/ethinyl estradiol transdermal system)

Amendment to a Pending
Application:
Response to FDA Request for
Chemistry, Manufacturing and

Controls (CM&C) Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180, submitted on 21 December 2000, for ORTHO EVRATM, a norelgestromin and ethinyl estradiol transdermal system. Reference is also made to our teleconference with the Division on 09 November 2001. During this teleconference, FDA requested the following:

•The proposed 8-hour dissolution specifications are too wide. An Excel spreadsheet containing the data from clinical batches 01107, 01517 and 01607 is requested.

•The development history for the dissolution method is requested. Specifically, we are interested in your rationale for the choice of medium and pH utilized in the specification.

Our responses and supporting data are provided behind the tabs entitled "Responses", "Appendix 1" and "Appendix 2". We have provided the best quality copies available. In addition, we have enclosed the Excel spreadsheet data on a diskette and forwarded an electronic copy via email to Jennifer Mercier, Project Manager, DRUDP. The diskettes were scanned using McAfee virus shield version V.4.5.0.534, virus definition 4.0.4169, scan engine 4.1.40 and deemed to be virus-free.

Should you have any questions and/or comments, please contact me directly at (908) 704-4812, call Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

The R.W. Johnson Pharmaceutical Research Institute

Ramon Polo, PhD

Director

**Regulatory Affairs** 

Send desk copies to:

1. Dr. Amit Mitra, Chemistry Reviewer

2. Dr. Dhriba J. Chatterjee, Biopharm. Reviewer

FDA/DRUDP

HRD-580

Rockville: MD 20857

Phone No. (301) 827-4260

#### **DEPARTMENT OF HEALTH AND HUMAN SERVICES** .\_\_ FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

Form Approved: OMB No. 0010-0338 Expiration Date: Merch 31, 2003 See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

(Title 21, Code of Federal Regulations, 314 & 601		
APPLICANT INFORMATION		
NAME OF APPLICANT The R.W. Johnson Pharmaceutical Research Institute	DATE OF SUBMISSION	······································
TELEPHONE NO. (Include Area Code)	FACSIMILE (FAX) Number (Include Area Code	)
(908) 704-4812	(908) 203-1499	<u> </u>
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code and U.S. Liberte number if previously issued):	AUTHORIZED U.S. AGENT NAME & ADDRESS ZIP Code, telephone & FAX number) IF APPLICA	(Number, Street, City, State, BLE
920 Route 202 South P.G. Box 300		
Raritan, New Jersey 08869-9602	·	
PRODUCT DESCRIPTION		
NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE	PPUCATION NUMBER (If previously inspect) NDA 2	1-180
ESTABLISHED NAME (e.g., Proper name, USPAUSAN name) noreignatromin and effiling estratiol	PROPRIETARY NAME (trade name) IF ANY ORTHO EVRA™	
CHEMICALIBIOCHEMICALIBLOOD PRODUCT NAME (I/ arty)	CODE NAME (# any)	
DOBAGE FORM: STRENGTHS: transdermel petch 6 mg noreigestromin 0.75 mg ethinyl estra	ROUTE OF ADMINISTRATION Transdormal	
(PROPOSED) MOICATION(S) FOR USE. Preprintion of Pregnancy		
PPLICATION INFORMATION		
APPLICATION TYPE (check one): NEW DRUG APPLICATION (21 CFR.914.50)   ABBI		)
FAMINDA; IDENTIFY THE APPROPRIATE TYPE   605 (b) (1)	□ 506 (b) (2)	
IF AMANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT. TI Name of Drug	AT IS THE BASIS FOR THE SUBMISSION	
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PROPOSED MARKETING STATUS (checkions) TOPRESCRIPTION PRODUCT		
	RX) OVER THE COUNTER PRODUCT (	отс)
NUMBER OF VOLUMES SUBMITTED THIS APPLICATION		C DELECTRONIC
ESTABLISHMENT INFORMATION (Full establishment should be provided in the Provide locations of all meralischings packaging and control sites for drug substance contact, satisfaces number, registration number (CFN), DMF number, and manufacturish. Please indicate whether the allie is ready for inspection or, if not, when it will be re-	and drug product (continuation sheets may be used if nece	esary), include name, address, billy testing) conducted at the
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Cos References (Set related Lourse Resilications, NOs, NOA, PMAs, 51000s.	DEs, BMFs, and DMFs referenced in the current appli-	
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П	Index     Labeling (check one)	☐ Draft Labeling	Final Printed Labeling
<del>-  </del>	3. Summary (21 CFR 314.50 (c))		
	Chemistry section		
_		d controls information (e.g. 21 CFR 314.50	(d) (1), 21 CFR 601.2)
		(1), 21 CFR 601.2 (a)) (Submit only upon F	
$\overline{\Box}$		e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601	
		dcology section (e.g. 21 CFR 314.50 (d) (2	
$\overline{\Box}$		svailability section (e.g. 21 CFR 314.50 (d)	
	7. Clinical Microbiology (e.g. 21 CFF		
	8. Clinical data section (e.g. 21 CFR		
		R 314.50 (d) (5) (vi) (b), 21 CFR 601.2)	
П	10. Statistical section (e.g. 21 CFR 3		
	11. Case report tabulations (e.g. 21 C	·····	
	12. Case reports forms (e.g. 21 CFR		
П	13. Patent Information on any patent	which claims the drug (21 U.S.C 355 (b) or	(c))
П		to any patent which claims the drug (21 U.	
	15. Establishment description (21 CF		
	16. Debarment certification (FD&C A	± 306 (k) (1))	
П	17. Field copy cartification (21 CFR 3		
n	18. User Fee Cover Sheet (Form FD/		
	19. Financial Information (21 CFR Pa	nt 54)	
	20: OTHER (Specify) Respon	ise to FDA Request for CM&C Information	
1. 2. 3. 4. 5. 6. 7.	led by FDA. If this application is approve g. but not limited to the following: Good menufacturing practice regulation Biological establishment standards in 2 Labeling regulations in 21 CFR 201, 60 In the case of a prescription drug or blo Regulations on making changes in appl Regulations on reports in 21 CFR 314.1 Local, state and Federal environmental	ed, I agree to comply with all applicable law us in 21 CFR 210 and 211, 806 and/or 820. 1 CFR Part 600. 8, 610, 660 and/or 809. logical product, prescription drug advertish lication in 21 CFR 314.70, 314.71, 314.72, 30, 314.81, 600.80 and 600.81. Impact laws.	ng regulations in 21 CFR 202.
product The da Westplin Signat	turill the Drug Enforcement Administration and Information in this submitted on having a willfully false simplement is a crimina TURE OF RESPONSIBLE OFFICIAL OR A Music Property of the Contract of the Contr	ion makes a final acheduling decision. ve been reviewed and, to the best of my kn al offense, U.S. Code, title 18, section 1001	iowledge are certified to be true and accurate.
ADDRE	SS (Smeet City, Steel, and ZIP Code) 820 Route 282 Scient, P.O. Box Rantan, New Jorgan, 1886, 080	300	Telephone Number (908) 704-4812

Instructions searching executes courses, gamening and maintaining the data needed, and comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing burden to:

An agency may not conduct or sponsor, and a

earment of Fleetin and Human Services rood and Drug Administration CBER, HFM-99 1401 Rockylle Pike Rockylle MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

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### THE R.W. JOHNSON PHARMACEUTICAL RESEARCH INSTITUTE

920 U.S. Route # 202, P.O. Box 300 Raritan, New Jersey 08869-602

### TELEFACSIMILE TRANSMITTAL FORM

FAX NUMBER: (908) 203-1499

13 November 2001

JENNIFER MERCIER

Project Manager, FDA

Div. Reprod. & Urol. Drug Products

FROM: Valerie Donne

Regulatory Affairs Phone: (908) 704-5891

Fax: (908) 203-1499

TELEFAX #

(301) 827-4267

NUMBER OF PAGES (INCLUDING TRANSMITTAL FORM):

44

TOTAL

NOTE. If you do not receive the correct number of pages or if the transmission is unclear, please call me at (908) 704-5891.

plus 2 com sheets

#### MESSAGE (If my):

JENNIFER RE NDA 21-180 ORTHO EVRATM dissolution date

ATTACHED IS A FAXED VERSION OF OUR RESPONSE TO THE AGENCY'S 09 NOVEMBER 2001 REQUEST TO PROVIDE ADDITIONAL CM&C INFORMATION. A hard copy submission will follow tumorrow massing. If you have additional questions or comments on this submission, please call me at (208) 704-5881. THANKYOU

#### **CONFIDENTIALITY NOTICE**

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# THE R.W. JOHNSON PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

**DESK COPY** 

0 2 NOV 2001

Dr. Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug
Product

Attn.: Document Control Room 14B-04 5600 Fishers Lane Rockville, Maryland 20857-1706 NDA 21-180
ORTHO EVRATM
(norelgestromin/ethinyl estradiol transdermal system)

General Correspondence: Response to FDA Request For Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180 for ORTHO EVRA<sup>TM</sup>, a norelgestromin (NGMN) and ethinyl estradiol (EE) transdermal contraceptive system, submitted on 20 December 2000. We are providing information at this time as per Dr. Chatterjee's 18 October 2001 email request. The FDA question appears below in bold face type and the RWJPRI response appears below it.

Question: Does the sponsor have any data information regarding the residual amount of drug content in the patches after use (7 days), or any data that indicates what % of the loaded drug is released from the patch on to the skin in 7 days (not just what is bioavailable)?

#### Response:

Tables 1-3 show the data requested by the reviewer. The data were generated by analyzing patches from human subjects for norelgestromin (NGMN) and ethinyl estradiol (EE), after the patches had been worn for 7 days. The apparent quantity of drug delivered (in % Formula Strength) was calculated by subtracting the quantity of drug remaining in the patch from the quantity in the control (unused patches). For study NRGEEP-PHI-003, the quantity of drug in the control patches was determined in a separate assay while for studies NRGEEP-PHI-004 and NRGEEP-PHI-005, the batch release assay values were used as the "control."

.\110201 response to fda req biopharm info doc

Tables 1-3 show the data available from the three studies cited above after 7 days of treatment. For studies NRGEEP-PHI-003 and -005, the patch was worn on the abdomen while for study NRGEEP-PHI-004, the patch was worn on different areas of the body (upper outer arm, abdomen, upper torso or buttock) as indicated in Table 2.

On examination of the data, it is clear that there is considerable variability in the data for apparent amounts of each drug delivered. For example, considering only the abdomen as the application site, the average apparent amounts of drug delivered (in the three studies) range from 164.6 to 276.9 µg/day for NGMN and from 29.9 to 42.9 µg/day for EE. When one includes the standard deviations, the range is 119.2 to 387.5 µg/day for NGMN and 19.1 to 60.9 µg/day for EE. Therefore, it is difficult to draw any firm conclusions on the true amount of drug delivered to the systemic circulation from these data. Our opinion is that the calculated apparent amount of drug delivered is, at best, a crude method of determining how much drug is actually delivered from the patch to the surface of the skin and does not reflect either the absolute dose delivered to the systemic circulation or the relative dose comparable to an oral contraceptive tablet.

At the time these determinations were done, they were being used as a development tool to help assess our progress in achieving the target quantities of actives in the patch and in the systemic circulation. They were not done in an attempt to achieve mass balance, which is a much more demanding and difficult exercise. For example, the skin was not swabbed and any residual adhesive collected to account for drug on the skin at the time the patch was removed. For these reasons, we are of the opinion that the data provided here represent estimates of the apparent amounts of delivered drug to the surface of the skin, and do not accurately reflect the quantity of each drug delivered into the circulation.

In the past, "difference" methods, which indirectly estimated the daily dose have been used. Doses were estimated, by difference, via subtraction of the residual amounts in the patch following removal after wear, from the amount of drug(s) present from unused patches, added to that extracted from the skin. Even with such precautions, such methods tend to be highly variable, and could lead to inaccurate estimations of the amount of drug delivered systemically. Such variability stems from the variability in patch extraction, skin extraction, and the large difference between what is actually in the patch and the small amount delivered per day.

The shortcomings of this approach were discussed with the agency on August 31, 1998 and, at the time, the more direct approach of determining the dose delivered to the systemic circulation (described in draft protocol of NRGEEP-PHI-014 submitted to the agency) was deemed acceptable. It was subsequently performed as study NRGEEP-PHI-014, a report of which was submitted in the NDA (Item 6/Item Volumes 2-3/Page1).

Table 1: Residual Drug Content Data From Study No. NRGEEP-PHI-003 ( Lot 00096) Following One Week of Wear on the Abdomen

	% Remaining (% FS)			
Subject <sup>a</sup>	Norelgestromin	Ethinyl estradiol		
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Mean (sd)	79.4 (±5.3)	70.3 (±10.1)		
		<del></del>		
Control (6 unused samples)	NGMN (% FS)	EE (% FS)		
Mean	98.6	98.2		
	NGMN (% FS)	EE (% FS)		
% "delivered" in 7 days	19.2 (±5.3)	27.9 (±10.1)		
70 delivered in 7 days	17.2 (±3.3)	1 21.5 (±10.1)		
	NGMN (μg)	EE (μg)		
Amount "delivered" per day	164.6* (±45.4)	29.9** (±10.8)		

<sup>&</sup>lt;sup>a</sup> The subject numbers as presented are internal code numbers which correspond to three digit subject numbers in the study report.

<sup>\*</sup> Sample calculation:  $19.2 \times 6000 \,\mu\text{g/}(100 \times 7 \,\text{days}) = 164.6 \,\mu\text{g/day}$ 

<sup>\*\*</sup> Sample calculation:  $27.9 \times 750 \,\mu\text{g}/(100 \times 7 \,\text{days}) = 29.9 \,\mu\text{g/day}$ 

	Drug Content D			% Remaini	ng (% FS)	, Following Or		
Subject		Norelges	tromin			Ethinyl es	stradiol	
	Outer Arm	Abdomen	Torso	Buttock	Outer Arm	Abdomen	Torso	Buttock
Mean:(sd)	67.1 (±7.9)	65.6	62.8	65.2 (±8.4)	56.0	55.4	50.4	52.9
<u> </u>	1	(±12.9)	(±11.8)	L	(±10.4)	(±16.8)	(±14.4)	(±13.5)
Control (Batch Release) Assay Result		NGMN 97.	(% FS) 9%			EE (9	% FS) 4%	
	T	NGMN	(% FS)	··· · · · · · · · · · · · · · · · · ·	<del></del>	EE (9	% FS)	
% "delivered"	30.8	32.3	35.1	32.7	39.4	40.0	45.0	42.5
in 7 days	(±7.9)	(±12.9)	(±11.8)	(±8.4)	(±10.4)	(±16.8)	(±14.4)	(±13.5)
					<del></del>			
-	<b>-</b> ,	NGM	N (μg)		<del> </del>	EE	(μg)	<del></del>
Amount "delivered" per	- 264.0 (±67.7)	276.9 (±110.6)	300.9 (±101.2)	280.3 (±72.0)	42.2 (±11.2)	42.9 (±18.0)	48.2 (±15.4)	45.5 (±14.5)

<sup>&</sup>lt;sup>4</sup> The subject numbers as presented are internal code numbers which correspond to three digit subject numbers in the study report.

<sup>b</sup> Patient 37 replaced Patient 21, who withdrew from the study.

ND = Not Determined

Table 3: Residual Drug Content Data From Study No. NRGEEP-PHI-005 Lot 00636) Following One Week of Wear on the Abdomen

	% Remain	ing (% FS)
Subject <sup>a</sup>	Norelgestromin	Ethinyl estradiol
19400	<del></del>	٥٠,٠٠
Control (Batch Release)	NGMN (% FS)	EE (% FS)
Assay Result	97.9	95.4
		<del></del>
	NGMN (% FS)	EE (% FS)
% "delivered" in 7 days	29.7 (±5.8)	35.8 (±7.7)
	NGMN (μg)	EE (μg)
Amount "delivered" per day	254.6 (±49.7)	38.4 (±8.2)

<sup>&</sup>lt;sup>a</sup> The subject numbers as presented are internal code numbers which correspond to three digit subject numbers in the study report.

Should you have any questions and/or comments, please contact me at (908) 704-4812, contact Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

The R.W. Johnson Pharmaceutical Research Institute

Ramon Polo, PhD

Director

Regulatory Affairs

Send 1 desk copy to Dr. Dhruba J Chatterjee, FDA/DRUDP/HFD-580

#### DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338 Expiration Date: March 31, 2003 See OMB Statement on page 2.

# APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

FOR FDA USE ONLY APPLICATION NUMBER

NAME OF APPLICANT The R.W. Johnson Pharmaceutic TELEPHONE NO. (Include Area Code) (908) 704-4812  APPLICANT ADDRESS (Number, Street, City, State and U.S. License number if previously issued): 920 Route 202 South P.O. Box 300 Raritan, New Jersey 08869-0602  PRODUCT DESCRIPTION  NEW DRUG OR ANTIBIOTIC APPLICATION NUM	te, Country, ZIP Code or Mail Code,	(908)	PAX) Number (Include Area Code)  203-1499  J.S. AGENT NAME & ADDRESS (Number, Street, City, Strong & FAX number) IF APPLICABLE
(908) 704-4812  APPLICANT ADDRESS (Number, Street, City, State and U.S. License number if previously issued):  920 Route 202 South P.O. Box 300 Raritan, New Jersey 08869-0602	·	(908)	) 203-1499 J.S. AGENT NAME & ADDRESS (Number, Street, City, St
APPLICANT ADDRESS (Number, Street, City, State and U.S. License number if previously issued):  920 Route 202 South P.O. Box 300 Raritan, New Jersey 08869-0602	·	, AUTHORIZED (	J.S. AGENT NAME & ADDRESS (Number, Street, City, St
ond U.S. License number if previously issued):  920 Route 202 South P.O. Box 300 Raritan, New Jersey 08869-0602 PRODUCT DESCRIPTION	·		
P.O. Box 300 Raritan, New Jersey 08869-0602 PRODUCT DESCRIPTION	?		
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		<del></del>	<del></del>
	MBER, OR BIOLOGICS LICENSE A	APPLICATION NUMBER	R (If previously issued) NDA 21-180
STABLISHED NAME (e.g., Proper name, USP/U norelgestromin and ethinyl estradio		PROPRIETARY NAM	E (trade name) IF ANY
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NA	AME (if any)		CODE NAME (If any)
DOSAGE FORM:	STRENGTHS:		ROUTE OF ADMINISTRATION:
transdermal patch	6 mg norelgestromin 0.75 mg ethinyl estra	diol	Transdermal
PLICATION INFORMATION  PLICATION TYPE  Check one) NEW DRUG APPLICATION	ION (21 CFR 314.50)	REVIATED APPLICATION	ON (ANDA. AADA, 21 CFR 314.94)
☐ BIOLOG	GICS LICENSE APPLICATION (21	CFR part 601)	
F AN NDA, IDENTIFY THE APPROPRIATE TYPE	E 505 (b) (1)	505 (b) (2)	
F AN ANDA, OR AADA, IDENTIFY THE REFERE Name of Drug	ENCE LISTED DRUG PRODUCT T Holder of Approve		R THE SUBMISSION
TYPE OF SUBMISSION (check one)	RIGINAL APPLICATION	AMENDMENT TO A PE	ENDING APPLICATION
☐ PRESUBMISSION ☐ ANNUAL REI	PORT EST	TABLISHMENT DESCRIPT	ION SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CH	HEMISTRY MANUFACTURING AND CO	ONTROLS SUPPLEMENT	<b>⊠</b> OTHER
F A SUBMISSION OR PARTIAL APPLICATION, I	PROVIDE LETTER DATE OF AGR	REEMENT TO PARTIAL	SUBMISSION:
F A SUPPLEMENT, IDENTIFY THE APPROPRIA	ATE CATEGORY   CBE	☐ CBE-30	Prior Approval (PA)
REASON FOR SUBMISSION RESPONSE TO I	FDA REQUEST FOR INFORMATI	ION	
PROPOSED MARKETING STATUS (check one)	PRESCRIPTION PRODUCT	(Rx)	OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED	THIS APPLICATION	IS PAPER	PAPER AND ELECTRONIC   ELECTRONIC
ESTABLISHMENT INFORMATION (Full establis Provide locations of all manufacturing, packaging a address, contact, telephone number, registration n conducted at the site. Please indicate whether the	and control sites for drug substance number (CFN), DMF number, and m	e and drug product (continuantification)	on.) inuation sheets may be used if necessary). Include name, for type of testing (e.g. Final dosage form, Stability testing)
ss References (list related License Application	tions, INDs, NDAs, PMAs, 510(k)	s, IDEs, BMFs, and DM	IFs referenced in the current application)
	<u>-</u>		

				•						
This ap	pplication contains the following items: (Check a	ill that apply)								
	1. Index									
<u> </u>	2. Labeling (check one)	Draft Labeling	Final Printed Labeling							
٦	3. Summary (21 CFR 314.50 (c))									
	4. Chemistry section									
	A. Chemistry, manufacturing, and controls info	ormation (e.g. 21 CFR 314.50 (d) (1), 21	I CFR 601.2)							
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)									
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)									
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)									
	6. Human pharmacokinetics and bioavailability se	ction (e.g. 21 CFR 314.50 (d) (3), 21 Ci	FR 601.2)							
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (	4))								
$[\Box]$	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5	i), 21 CFR 601.2)		<del></del>						
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)									
П	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)									
	11. Case report tabulations (e.g. 21 CFR 314.50 (f)	(1), 21 CFR 601.2)								
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2).	21 CFR 601.2)								
	13. Patent information on any patent which claims	the drug (21 U.S.C 355 (b) or (c))								
	14. A patent certification with respect to any patent	which claims the drug (21 U.S.C 355 (t	o) (2) or (j) (2) (A))	ę						
	15. Establishment description (21 CFR Part 600, if	· · · · · · · · · · · · · · · · · · ·		•						
	16. Debarment certification (FD&C Act 306 (k) (1))			:						
	17. Field copy certification (21 CFR 314.50 (k) (3))			<del></del>						
	18. User Fee Cover Sheet (Form FDA 3397)			·						
٦	19. Financial Information (21 CFR Part 54)									
	20. OTHER (Specify) RESPONSE TO FDA R	EQUEST FOR INFORMATION								
l agree warning request includir 1. 2.	IFICATION  to to update this application with new safety information ups, precautions, or adverse reactions in the draft label sted by FDA. If this application is approved, I agree to ung, but not limited to the following:  Good manufacturing practice regulations in 21 CFR 2 Biological establishment standards in 21 CFR Part 6	ing. I agree to submit safety update reposomply with all applicable laws and regulated and 211, 606 and/or 820.	orts as provided for by regulation of	or as						
1 3	Labeling regulations in 21 CER 201, 606, 610, 660 a	3 Labeling regulations in 21 CER 201, 606, 610, 660 and/or 809								

- 4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
- 5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
- 6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
- 7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate. Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT TYPED NAME AND TITLE Ramon Polo, PhD **Director, Regulatory Affairs** 

0 2 NOV 2001

ADDRESS (Street, City, State, and ZIP Code)

920 Route 202 South, P.O. Box 390 Raritan, New Jersey 08869-0602

Telephone Number (908) 704-4812

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing his burden to:

partment of Health and Human Services rood and Drug Administration CBER. HFM-99 1401 Rockville Pike Rockville, MD 20852-1448

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# THE R.W. JOHNSON PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug
Products

Attn.: Document Control Room 14B-04 5600 Fishers Lane Rockville, Maryland 20857-1706 NDA 21-180
ORTHO EVRA™
(norelgestromin/ethinyl estradiol transdermal system)

Amendment to a Pending Application:
Request for Marketing Exclusivity

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180, submitted on 21 December 2000, for ORTHO EVRATM, a norelgestromin and ethinyl estradiol transdermal system. Reference is also made to 21 CFR 314.50 (j) Claimed Exclusivity.

The R.W. Johnson Pharmaceutical Institute is claiming marketing exclusivity under 21 CFR 314.108 (b)(2). We hereby certify, to the best of our knowledge, this drug has not previously been approved under section 505(b) of the act containing any active moiety in the drug for which we are seeking approval.

Should you have any questions and/or comments, please contact me directly at (908) 704-4812, call Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

The RW Johnson Pharmaceutical Research Institute

Ramon Polo, PhD

Director, Regulatory Affairs

WEARLISEARESO!

#R/090301 cmc emand.doc/05 November 2001/kf



### THE R.W. JOHNSON PHARMACEUTICAL RESEARCH INSTITUTE

920 Route 202, P.O. Box 300 Raritan, NJ 08869-0602

### **Fax Cover Sheet**

Date:

November 8, 2001

Pages:

02

To:

Jennifer Mercier

From:

Karen Futterknecht

Dept.:

**FDA** 

Dept.:

**Regulatory Affairs** 

Fax #:

301-827-4267

Telephone #: 301-827-4249 Fax #:

908-722-5113

**Telephone #: 908-704-4912** 

Comments:

Dear Jennifer,

Attached is our request for marketing exclusivity.

Best regards,

# THE EWIOHNSON THARMACEUTICAL RESEARCH

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSE - 36863-0603



EM OF

Dr. Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug
Product
Attn.: Document Control Room 14B-04

Attn.: Document Control Room 14B-04 5600 Fishers Lane Rockville, Maryland 20857-1706 NDA 21-180
ORTHO EVRATM
(norelgestromin/ethinyl estradiol transdermal system)

General Correspondence: Response to Request for CM&C Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180 for ORTHO EVRA<sup>TM</sup>, a norelgestromin (NGMN) and ethinyl estradiol (EE) transdermal contraceptive system, submitted on 20 December 2000. At this time we wish to provide additional CM&C information as requested by the CMC Reviewer in an email message dated 29 October 2001. This letter is formatted with the FDA request in **boldface** type followed by RWJPRI's response.

### Chemistry, Manufacturing and Controls Information:

The Chemistry Reviewer's email stated, "I still need the items below to complete my review":

1. Revised specification sheets for norelgestromin and ethinyl estradiol.

The revised specification sheets for norelgestromin and ethinyl estradiol are provided behind the Attachment titled, "Revised Specifications/NGMN & EE".

2. Test method and acceptance criteria for polyethylene terephthalate and

The requested test method and acceptance criteria were mailed to FDA on 30 October 2001, directly from the supplier of the backing material, also faxed this information directly to FDA on 31 October 2001. This information was sent to the attention of Dr. Susan Allen at the DRUDP.

3. The storage conditions on pouch, carton and packer tray labels should be changed as follows: "Store at controlled temperature at 25 C, excursion permitted to 15-30 C.

LTR/110101cmc resp to fda req info doc/01 November 2001/JU

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RWJPRI agrees to revise the storage conditions as requested by FDA. We will however, change the word "excursion" to "excursions".

4. The picture of the dancing woman on all labels provided in amendment dated 05 October 2001, should be removed.

Although we acknowledge this request, RWJPRI believes that this logo should remain on the packaging components provided on 05 October 2001. Similar to other contraceptive and hormone replacement products on the market, we believe that the dancing woman is acceptable and does not warrant removal.

5. The established name of the drug product, "norelgestromin/ethinyl estradiol transdermal system" on pouch and carton labels fin the amendment dated 05 October 2001, should be printed darker for ease of reading.

RWJPRI agrees to print the requested text darker for ease of reading.

Should you have any questions and/or comments, please contact me at (908) 704-4812, contact Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

The R.W. Johnson Pharmaceutical Research Institute

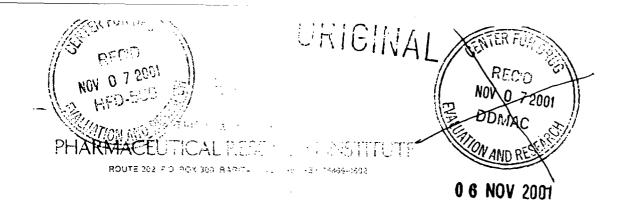
Ramon Polo, PhD

Director

Regulatory Affairs

cc: Desk copy to Dr. Amit Mitra, CM&C Reviewer HFD-580

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Dr. Susan Allen, MD, Director Food and Drug Administration Center for Drug Evaluation and Research Office of Drug Evaluation III, (HFD-580) Division of Reproductive and Urologic Drug

Attn.: Document Control Room 14B-04 5600 Fishers Lane Rockville, Maryland 20857-1706

NDA 21-180 ORTHO EVRATM (norelgestromin/ethinyl estradiol transdermal system)

Amendment to a Pending Application:

Response to FDA Request For CM&C Information

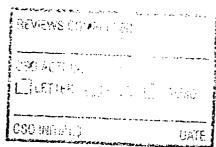
Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180 for ORTHO EVRATM, a norelgestromin (NGMN) and ethinyl estradiol (EE) transdermal contraceptive system, submitted on 20 December 2000. Reference is also made to the Chemistry Reviewer's 02 November 2001 request to revise the storage conditions of the drug product. At this time we wish to amend the NDA with the following response. The FDA request appears below in bold face type and the RWJPRI response follows.

As per the stability guidance, please revise the storage conditions on the pouch, carton, and packer trays to add the equivalent degrees in Farenheit to the temperatures listed. The statement should read, "Store at controlled temperature at 25 °C (77 °F), excursions permitted to 15-30 °C (59-86 ° F)."

RWJPRI agrees to make the change to the storage conditions as described above to the packaging components. In addition, to remain consistent, the USPI will be revised in the same manner and submitted during label negotiations with the Agency.

Should you have any questions and/or comments, please contact me at (908) 704-4812, contact Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.



TR\110601 response to fda req CMC info.doc/06 November 2001/JU/1

SPRING HOUSE

Sincerety,

The R.W. Johnson Pharmaceutical Research Institute

Ramon Polo, PhD

Director

Regulatory Affairs

Send 1 desk copy to: Dr. Amit Mitra, FDA/DRUDP/HFD-580, Reviewing Chemist



THE RIW JOHNSON

PHARMACEUTICAL RESEARCH INSTITUT

300/15 202, 8.0 BUX 20 BARTAN, NEW JERSEY 08859-0502

REPORT OF THE HAD COME.

0 2 NOV 2001

ORIG AMENDMENT

Dr. Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug
Product

Product
Attn.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180
ORTHO EVRATM
(norelgestromin/ethinyl estradiol transdermal system)

General Correspondence: Response to FDA Request For Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180 for ORTHO EVRA<sup>TM</sup>, a norelgestromin (NGMN) and ethinyl estradiol (EE) transdermal contraceptive system, submitted on 20 December 2000. We are providing information at this time as per Dr. Chatterjee's 18 October 2001 email request. The FDA question appears below in bold face type and the RWJPRI response appears below it.

Question: Does the sponsor have any data information regarding the residual amount of drug content in the patches after use (7 days), or any data that indicates what % of the loaded drug is released from the patch on to the skin in 7 days (not just what is bioavailable)?

### Response:

Tables 1-3 show the data requested by the reviewer. The data were generated by analyzing patches from human subjects for norelgestromin (NGMN) and ethinyl estradiol (EE), after the patches had been worn for 7 days. The apparent quantity of drug delivered (in % Formula Strength) was calculated by subtracting the quantity of drug remaining in the patch from the quantity in the control (unused patches). For study NRGEEP-PHI-003, the quantity of drug in the control patches was determined in a separate assay while for studies NRGEEP-PHI-004 and NRGEEP-PHI-005, the batch release assay values were used as the "control."

N Vagar Virvi 10201 response to Ida req biopharm info doc LA JOLLA RARITAN Tables 1-3 show the data available from the three studies cited above after 7 days of treatment. For studies NRGEEP-PHI-003 and -005, the patch was worn on the abdomen while for study NRGEEP-PHI-004, the patch was worn on different areas of the body (upper outer arm, abdomen, upper torso or buttock) as indicated in Table 2.

On examination of the data, it is clear that there is considerable variability in the data for apparent amounts of each drug delivered. For example, considering only the abdomen as the application site, the average apparent amounts of drug delivered (in the three studies) range from 164.6 to 276.9 µg/day for NGMN and from 29.9 to 42.9 µg/day for EE. When one includes the standard deviations, the range is 119.2 to 387.5 µg/day for NGMN and 19.1 to 60.9 µg/day for EE. Therefore, it is difficult to draw any firm conclusions on the true amount of drug delivered to the systemic circulation from these data. Our opinion is that the calculated apparent amount of drug delivered is, at best, a crude method of determining how much drug is actually delivered from the patch to the surface of the skin and does not reflect either the absolute dose delivered to the systemic circulation or the relative dose comparable to an oral contraceptive tablet.

At the time these determinations were done, they were being used as a development tool to help assess our progress in achieving the target quantities of actives in the patch and in the systemic circulation. They were not done in an attempt to achieve mass balance, which is a much more demanding and difficult exercise. For example, the skin was not swabbed and any residual adhesive collected to account for drug on the skin at the time the patch was removed. For these reasons, we are of the opinion that the data provided here represent estimates of the apparent amounts of delivered drug to the surface of the skin, and do not accurately reflect the quantity of each drug delivered into the circulation.

In the past, "difference" methods, which indirectly estimated the daily dose have been used. Doses were estimated, by difference, via subtraction of the residual amounts in the patch following removal after wear, from the amount of drug(s) present from unused patches, added to that extracted from the skin. Even with such precautions, such methods tend to be highly variable, and could lead to inaccurate estimations of the amount of drug delivered systemically. Such variability stems from the variability in patch extraction, skin extraction, and the large difference between what is actually in the patch and the small amount delivered per day.

REVIEWS COMPLETED

CSO INITIALS

DATE

The shortcomings of this approach were discussed with the agency on August 31, 1998 and, at the time, the more direct approach of determining the dose delivered to the systemic circulation (described in draft protocol of NRGEEP-PHI-014 submitted to the agency) was deemed acceptable. It was subsequently performed as study NRGEEP-PHI-014, a report of which was submitted in the NDA (Item 6/Item Volumes 2-3/Page1).

APPEARS THIS WAY ON ORIGINAL

N. Committee 110201 response to fda req biopharm info doc

Table 1: Residual Drug Content Data From Study No. NRGEEP-PHI-003 ot 00096) Following One Week of Wear on the Abdomen

	% Remaining (% FS)			
Subject <sup>a</sup>	Norelgestromin	Ethinyl estradiol		
		!		
		<del></del>		
	70.4(15.3)	70.2 (110.1)		
Mean (sd)	79.4 (±5.3)	70.3 (±10.1)		
Control (6 unused samples)	NGMN (% FS)	EE (% FS)		
Mean	98.6	98.2		
	NGMN (% FS)	EE (% FS)		
% "delivered" in 7 days	19.2 (±5.3)	27.9 (±10.1)		
	NOVOL	FF ()		
A	NGMN (μg)	EE (μg)		
Amount "delivered" per day	164.6* (±45.4)	29.9** (±10.8)		

<sup>&</sup>lt;sup>a</sup> The subject numbers as presented are internal code numbers which correspond to three digit subject numbers in the study report.

<sup>\*</sup> Sample calculation:  $19.2 \times 6000 \, \mu g/(100 \times 7 \, days) = 164.6 \, \mu g/day$ \*\* Sample calculation:  $27.9 \times 750 \, \mu g/(100 \times 7 \, days) = 29.9 \, \mu g/day$ 

						<u> </u>			
Subject		Norelgestromin			<del></del>	Ethiny	estradiol		
	Outer Arm	Abdomen	Torso	Buttock	Outer Arm	Abdomen	Torso	Buttock	
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Mcan (sd)	67.1 (±7.9)	65.6	62.8	65.2 (±8.4)	56.0	55.4	50.4	52.9	
		(±12.9)	(±11.8)	30.2 (20.1)	(±10.4)	(±16.8)	(±14.4)	(±13.5)	
Control							\	(6.0.5)	
Control atch Release	.						- <del></del>		
ssay Result	<del>'  </del>	NGMN (% FS)		EE (% FS)					
	<del></del>	97.	9%		l	95.	4%		
	T	NGMN	(% FS)	<del></del>					
"delivered"	30.8	32.3	35.1	32.7	10 4	EE (9			
ın 7 days	(±7.9)	(±12.9)	(±11.8)	(±8.4)	39,4 (±10.4)	40.0	45.0	42.5	
			1	(±0.4)	(±10.4)	(±16.8)	(±14.4)	(±13.5)	
	₹.	NGM	N (μg)		<del></del>	EE	(ua)		
Amount				1 322.3					
livered" per		276.9	300.9	280.3	42.2	42.9	48.2	45.5	
day	(±67.7)	(±110.6)	(±101.2)	(±72.0)	(±11.2)	(±18.0)	(±15.4)	(±14.5)	

<sup>\*</sup> The subject numbers as presented are internal code numbers which correspond to three digit subject numbers in the study report.

\*Patient 37 replaced Patient 21, who withdrew from the study.

\*ND = Not Determined

Table 3: Residual Drug Content Data From Study No. NRGEEP-PHI-005 / Lot 00636) Following One Week of Wear on the Abdomen

	% Remaining (% FS)		
Subject <sup>a</sup>	Norelgestromin	Ethinyl estradiol	
Mean (sd)	68.2 (±5.8)	59.6 (±7.7)	
Control (Batch Release) Assay Result	NGMN (% FS) 97.9	EE (% FS) 95.4	
% "delivered" in 7 days	NGMN (% FS) 29.7 (±5.8)	EE (% FS) 35.8 (±7.7)	
Amount "delivered" per day	NGMN (μg) 254.6 (±49.7)	EE (μg) 38.4 (±8.2)	

<sup>&</sup>lt;sup>a</sup> The subject numbers as presented are internal code numbers which correspond to three digit subject numbers in the study report.

Should\_you have any questions and/or comments, please contact me at (908) 704-4812, contact Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

The R.W. Johnson Pharmaceutical Research Institute

Ramon Polo, PhD

Director

Regulatory Affairs

Send 1 desk copy to Dr. Dhruba J Chatterjee, FDA/DRUDP/HFD-580

SUBMISSION FOX CO

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# THE RIKE TOFINSON PHARMACEUTICAL RESEARCH FAIR THE FAIR

ROUTE 202, P.O. SOA 389, RARITAN, NEW JERSEY 38529-74, J

# NDA ORIG AMENDMENT N - 13/2

Susan Allen, MD, Director Division of Reproductive and Urologic Drug Products HFD-580

HOMAL

Center for Drug Evaluation and Research Food and Drug Administration Attn.: Document Control Room 14B-04

5600 Fishers Lane Rockville, Maryland 20857-1706 NDA 21-180 ORTHO EVRA™ (norelgestromin/ethinyl

estradiol transdermal system)

AMENDMENT TO A **PENDING APPLICATION:** 

Labels/Labeling Information and & Chemistry, Manufacturing Controls Information

Dear Dr. Allen:

Reference is made to our pending NDA 21-180 for ORTHO EVRA™ and to the draft package components submitted with the original application on 20 December 2000 NDA (Item 2, Item Volume 1, Pages 52-59). Reference is also made to the draft packaging components that were amended to the pending application on 05 October 2001. At this time we would like to amend the NDA with a revised packaging component for the finished drug product replacement patch. A copy of the replacement patch overwrap and carton are included in this submission. This amendment is being provided at this time in order to gain a preliminary review of the text and text formatting planned.

Please note that these components were prepared prior to receiving Dr. Mitra's 29 October 2001 comments on the packaging components that were submitted to the Agency on 05 October 2001. Thus, as agreed, we will darken the text on the established name of the drug product, "norelgestromin/ethinyl estradiol transdermal system" on this replacement patch pouch and carton and revise the storage conditions to reflect, "store at controlled temperature at 25° C, excursions permitted to 15 - 30° 

#### Labels/Labeling Information Enclosed:

- One black and white copy of the pouch overlabel to be applied to replacement pouches (quantity 1)
- One color copy of the replacement patch carton -Trade (quantity 1)

#### Chemistry, Manufacturing and Controls Information:

In addition, we would like to know if the CMC Reviewer has considered our 05 October and 12 October 2001 requests to include the two additional inactive

matter\10101 package comp amend & cmc status doc

LA JOLLA SPRING HOUSE **RARITAN** 

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ingredients, "polyester backing film laminate" and "polyester release liner" on the cartons but not on the pouch labels. Due to space limitations, we are not able to add this additional text to the pouch labels without jeopardizing the readability of the pouch text.

Lastly, in the 24 October 2001 submission, RWJPRI agreed to change the drug product appearance specification upon approval, to include the following sentence, "No change in surface area of the transdermal system should occur while removing the transdermal system from the pouch." We would like to know if the CMC Reviewer has reached a decision on our 24 October 2001 request to distribute, on approval, the batches that were manufactured prior to approval using the old appearance specification for the drug product.

If you have questions regarding this information please contact me at (908)-704-4812 or Valerie Donnelly at (908)-704-5891 or our dedicated number for FDA use (908)-704-4600.

Sincerely,

The RW Johnson Pharmaceutical Research Institute

Ramon Polo Ph.D.

Director

Regulatory Affairs

Send I desk copy to: Dr. Amit Mitra, FDA/DRUDP/HFD-580, Reviewing Chemist

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED	
OSO AUTOU:	☐ MEMO
CSO INITIALS	DATE

unitable package complamend & cmc status doc

# ORIG AMENDMENT

3 0 OCT 2001

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Grologic Drug
Product

Attn.: Document Control Room 14B-04 5600 Fishers Lane Rockville, Maryland 20857-1706

NDA 21-180 ORTHO EVRA [N] (norelgestromin/ethinyl estradiol transdermal system)

General Correspondence: Response to FDA Request For Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180 for ORTHO EVRA<sup>TM</sup>, a norelgestromin (NGMN) and ethinyl estradiol (EE) transdermal contraceptive system, submitted on 20 December 2000. We are providing information at this time as per the Biopharm Reviewer's requests received via email on 18 October 2001. The FDA question appears on the following pages in bold face type and the RWJPRI response appears after it. In addition, the last page of this submission contains a correction to the 12 October 2001 submission which contained responses to FDA's 27 September 2001, CM&C, Discipline Review Letter. We apologize for this error.

Should you have any questions and/or comments, please contact me at (908) 704-4812, contact Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

Ramon Polo, PhD

Director

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Regulatory Affairs

REVIEWS COMPLETED

Send I Desk Copy to: Dr. Amit Mitra, Reviewing Chemist

FDA/DRUDP HFD-580 Rockville, MD 20857 Phone No: (301) 827-4260 **6**7 is :-



# ORIG AMENDMENT

2 9 OCT 2001

Dr. Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug
Product

Attn.: Document Control Room 14B-04

5600 Fishers Lane

Rockville, Maryland 20857-1706

NDA 21-180 ORTHO EVRATM

(norelgostromin/ethinyl estradiol transdermal system)

General Correspondence:

Response to FDA Request For

Dear Dr. Allen:

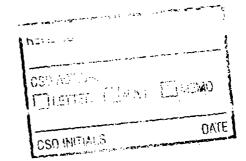
Reference is made to pending New Drug Application (NDA) 21-180 for ORTHO EVRATM, a norelgestromin (NGMN) and ethinyl estradiol (EE) transdermal contraceptive system, submitted on 20 December 2000. We are providing information at this time as per the Medical Reviewer's request received via email on 19 October 2001 and as per Ms. Mercier's request on 09 August 2001 (response number 8 for Subject No. 1181). The FDA question appears below in bold face type and the RWJPRI response appears below it.

1. Pregnancy outcomes for 15 on-therapy pregnancies and Subject 20018 (site 1025 in study 002).

This information is provided in the Four-Month Safety Update submitted 12 April 2001. Another copy of this update can be provided if necessary.

- 2. a. Site # for subject 21014 in study 002
  - b. Study, site#, subject# for subjects with the following SAEs:
  - Psychosis manic-depression
    Suicide attempt

See Attachment 1.



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- 3. For each of the following parameter listed below, please provide the mean, median, range and
  - a. # of days per cycle of expected bleeding/spotting during the drug-free interval
  - b. # of days per cycle of unexpected bleeding/spotting during the 21 day drug administration interval
  - c. total # of days of bleeding/spotting per cycle
  - d. duration of withdrawal bleeding (expected menses)

### See Attachment 2.

a. give the % of subjects per cycle with ≥ 7 days of bleeding and/or spotting
 b. give the % of subjects per cycle with > 10 days of bleeding and/or spotting

#### See Attachment 3.

- 5. a. per cycle, the % of subjects with amenorrhea (no withdrawal bleed during drug free interval)
  - b. per cycle, the % of subjects with amenorrhea for any 2 cycles (do not have to be consecutive)
  - c. per cycle, the % of subjects with amenorrhea for  $\geq 3$  cycles (do not have to be consecutive)

#### See Attachment 4.

- 6. a. % of subjects who reported at least 1 episode of breakthrough bleeding and/or spotting (BBT) at any time during the study
  - b. % of subjects with BBT in cycles 1-3
  - c. % of subjects with BBT in cycles 11-13

#### See Attachment 5.

7. Expected day of onset of withdrawal bleeding (menses) during drug free interval.

See Attachment 6.

Should you have any questions and/or comments, please contact me at (908) 704-4812, contact Valerie Donneity at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-1600.

Sincerely,

The R.W. Johnson Pharmaceutical Research Institute

Ramon Polo, PhD Director Regulatory Attairs

Desk copy to : Dr. Daniel Davis Medical Reviewer, DRUDP



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2 5 OCT 2001

Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproduction and Urologic Drug
Products

Attn.: Document Control Room 14B-04 5600 Fishers Lane Rockville, Maryland 20857-1706

NDA 21-180

Norelgestromin/Ethinyl Estradiol Transdermal System

NOA OF

Amendment to a Pending Application:

Response to Request for Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180, submitted on 20 December 2000, for a norelgestromin/ethinyl estradiol transdermal system. Reference is also made to Ms. Mercier's 09 August 2001 telephone call to request information and to a letter sent to FDA 09 October 2001 stating that we were working to obtain this information. The request for additional information was as follows:

 For study CONT-003, Subject No. 1181, the hospital discharge summary is requested.

Attached is a copy of the hospital discharge summary for this subject.

If you have any questions concerning this submission please call me at (908) 704-4812, call Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

Director

Regulatory Affairs

Desk copy to: Dr. Daniel Davis.

Medical Reviewer, DRUDP

CSO INTUALS DATE



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2 4 OCT 2001

PL

Dr. Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug
Product
Attn.: Document Control Room 14B-04
5600 Fishers Lane

NDA 21-180
ORTHO EVRATM
(norelgestromin/ethinyl estradiol transdermal system)

Attn.: Document Control Room 14B-04
5600 Fishers Lane

Rockville, Maryland 20857-1706

General Correspondence:
Response to FDA Request For Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180 for ORTHO EVRA<sup>TM</sup>, a norelgestromin (NGMN) and ethinyl estradiol (EE) transdermal contraceptive system, submitted on 20 December 2000. Reference is also made to the email requests from FDA received on 17 October 2001 and 19 October 2001. At this time, we are providing the information requested. The FDA request appears below in bold face type and the RWJPRI response appears below it.

#### 17 October 2001 CM&C Request:

The appearance specification of the drug product should include the following additional sentence to address the cold flow: "No change in surface area of the transdermal system should occur while removing the transdermal system from the pouch".

#### Response:

The Appearance specification will be changed to include the following sentence, "No change in surface area of the transdermal system should occur while removing the transdermal system from the pouch." This change will take effect upon approval and, as such, will apply to batches manufactured trom that point forward. In the interior, we would like to request permission from the Agency to distribute, on approval, the batches that were manufactured with the old appearance specification.

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# October 2001 FDA Question:

In a submission you mention a facility in regards to the bioequivalence but this facility is not listed in the NDA for a man and the submission what the intentions are regarding this facility?

Study NRGEEP-PHI-016 is a bioequivalence study and was conducted to evaluate a potential alternate manufacturer, for ORTHO-EVRA. As the conclusion of this study is non-equivalence between

ORTHO-EVRA patch is not relevant to the current NDA submission. Additional bioequivalence studies with modified — process patch lots are being conducted under subsequent to this NDA. Reports for these studies will be provided it necessary — will not be used as an alternate manufacture: this product unless bioequivalence is achieved and then, only after obtaining approval from the agency.

The pharmacokinetic data from the \_\_\_\_ patch portion of Study NRGEEP-PHI-016 is from the NDA clinical lot 01607 and is relevant to the current NDA. In addition, these data from the \_\_\_\_ clinical lot are included with pharmacokinetic data from other Phase 1 studies in a pooled database from which population pharmacokinetic analyses were conducted and included in the current NDA.

Should you have any questions and/or comments, please contact me at (908) 704-4812, contact Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

The R.W. Johnson Pharmaceutical Research Institute

Ramon Polo, PhD

Director

Regulatory Affairs



# THE R.W. JOHNSON PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602



1 5 OCT 2001

Dr. Susan Allen, MD, Director Food and Drug Administration Center for Drug Evaluation and Research Office of Drug Evaluation III, (HFD-580)

Division of Reproductive and Urologic DrugORIG AMENDMANT

Product

Attn.: Document Control Room 14B-04 5600 Fishers Lane Rockville, Maryland 20857-1706

General Correspondence:

Response to FDA Request for

NDA 21-180

ORTHO EVRATM

transdermal system)

(norelgestromin/ethinyl estradiol

CM&C Samples

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180 submitted on 21. December 2000, for ORTHO EVRATM, a norelgestromin (NGMN) and ethinyl: estradiol (EE) transdermal contraceptive system. At this time we wish to provide additional sample patches as per Dr. Amit Mitra's request to provide product that is either two years old or as close to the expiration date as possible.

# **Chemistry, Manufacturing and Controls Information:**

Enclosed are 19 samples of the ORTHO EVRATM transdermal contraceptive system. The patches are from lot number 00779 and the date of manufacture was 02 September 1999. This lot was made after the clinical trial lots and before the first PV lot, but underwent the same testing and QA scrutiny and batch record review as all of those lots. Please note that although these patches are not heat stamped with the trademark/dose, they do contain active ingredients and should be handled accordingly. For the purposes of this submission, the systems are sealed in a protective plastic bag.

Should you have any questions and/or comments, please contact me at (908) 704-4812, contact Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

Ramon Polo, PhD

Director

Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION:	
CSO INITIALS	DATE

Desk Copy to: Dr. Amit Mitra, CM&C Reviewer HFD-580

N \@FSt-R46\LTR\101501 2 yr patch samples .doc/15 October 2001/JU

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# THE R.W. JOHNSON PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

1 2 OCT 2001

Dr. Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug
Product

Attn.: Document Control Room 14B-04 5600 Fishers Lane Rockville, Maryland 20857-1706

NDA 21-180
ORTHO EVRATM
(norelgestromin/ethinyl estradiol transdermal system)

General Correspondence:
Response to FDA Request For CM&C Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180 for ORTHO EVRA<sup>TM</sup>, a norelgestromin (NGMN) and ethinyl estradiol (EE) transdermal contraceptive system, submitted on 20 December 2000. Reference is also made to the Discipline Review Letter received on 27 September 2001. At this time we wish to provide the following responses. The FDA question appears below in bold face type and the RWJPRI response follows.

#### **Drug Substance (norelgestromin)**

1.	Please submit the information on the type of bag used during stability studies
	of norelgestromin.

a. b.

2. Based on the ICH recommendations, the acceptance criteria for total impurities in the drug substance, norelgestromin should be tightened to unless justified.

Based on data from batches of norelgestromin manufactured in the years 1999 to 2001, we accept the limit for total impurities in norelgestromin to "Not More the supplier of this drug substance, will supply material that meets this specification.

A copy of the revised norelgestromin drug substance specification will be sent to the Agency as soon as it is available.

FALTR\101201 response to fda req CMC info.doe/12 October 2001/JU/1

# 3. \_\_\_\_\_ is deficient. A deficiency letter was sent to the DMF holder.

We are aware that a deficiency letter was sent to the DMF holder, however we believe the DMF number is actually as noted in the Discipline Review Letter.

# **Drug Substance (ethinyl estradiol)**

1. The acceptance criteria for total impurity for ethinyl estradiol related substances should be tightened to based on the analysis of the data provided, unless justified.

The impurities and degradation products in drug substance batches of ethinyl estradiol (EE) are controlled by two chromatographic purity tests,

Our acceptance criteria for test are in conformance with that monograph.

A copy of the revised drug substance specification will be submitted to the Agency as soon as it is available.

This information from is presented in Attachment 2. Please note that information about molecular weight and % solids is not supplied to—by the vendor.

2. Submit a certificate of analysis with coating weight and subsequent adhesion values, since those are parts of the specification.

A Certificate of Analysis from \_ / . . showing the coating weight and subsequent adhesion values is included in Attachment 3.

3. Provide labeling information of the jumbos and slit roll prior to shipping, and the storage conditions for the finished product.

Each liner roll is double-bagged and placed on pallets per the customer specification. The pallets are shrink wrapped. The packaged rolls are labeled with the product identity, lot number, quantity, manufacturer's name, and customer purchase order and part number. The rolls are stored in an air conditioned area until shipment.

The liner rolls should be stored indoors, preferably in an air conditioned warehouse area at temperatures not exceeding 90 °F and relative humidity in the 20-70% range.

Information on the packaging, labeling and storage is included at the end of the information provided in Attachment 2. A copy of a sample label roll and a sample packing slip for one pallet are provided in Attachment 4.

# Non woven backing film

-	• •
purchases the polyeth	ylene terephthalate and
	which is located to the
facility in '	The polymer chip is transferred through
nipelines or sent via railcar	from the ——— facility to the ———— facility

receives this material based on Certificates of Analysis for each polymer

1. Provide test methods and acceptance criteria of polyethylene terephthalate

# Number of Pages Redacted 5



Confidential, Commercial Information 3. Provide a disposal procedure for the transdermal patch in the "How Supplied" section, since the drug product, when disposed, would contain a large quantity of the residual drugs and it may pose hazard by accidental use.

RWJPRI proposes to copy the disposal procedure text that currently appears in the patient labeling of the NDA into the How Supplied section of the physician labeling. The text is as follows and may be found in the original NDA, Item 2/Item Volume1/Page47: "The used patch still contains some active hormonesthrow it away by carefully folding it in half so that it sticks to itself."

Should you have any questions and/or comments, please contact me at (908) 704-4812, contact Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

The R.W. Johnson Pharmaceutical Research Institute

Ramon Polo, PhD

Director

Regulatory Affairs

Send 1 desk copy to: Dr. Amit Mitra, FDA/DRUDP/HFD-580, Reviewing Chemist



1 1 OCT 2001

**ORIG AMENDMENT** 

1112

Dr. Susan Allen, MD, Director Food and Drug Administration Center for Drug Evaluation and Research Office of Drug Evaluation III, (HFD-580) Division of Reproductive and Urologic Drug **Product** 

Attn.: Document Control Room 14B-04 5600 Fishers Lane

Rockville, Maryland 20857-1706

Dear Dr. Allen:

2012 11 1 1 1 1 2 67

NDA 21-180 ORTHO EVRA™

(norelgestromin/ethinyl estradio) transdermal system)

General Correspondence: Response to FDA Request For Information

Reference is made to pending New Drug Application (NDA) 21-180 for ORTHO EVRATM, a norelgestromin (NGMN) and ethinyl estradiol (EE) transdermal contraceptive system, submitted on 20 December 2000. We are providing information at this time as per Dr. Chatterjee's 05 October 2001 email request. The FDA question appears below in bold face type and the RW... ....se appears below it.

#### **Ouestion:**

I am reviewing the dissolution information provided my section (6) of the NDA. and 01607 ... Was wondering whether the sponsor could confirm that these lots were identical to the phase 3 and the to-be-marketed lots.

#### Response:

Lots 01107, 01517 and 01607, were indeed the Phase 3 lots. The to-be-marketed lots meet NDA specifications that were developed by a procedure that included these three Phase 3 lots as well as other lots (for details, please see Section 3.6.3 of the NDA [Item 4/Item Volume 4/Page 24]). We believe this meets the reviewer's

•		Vor comments, please contact me at (908) 704- 08) 704-5891 or call our telephone line <u>dedicated</u>	
for FDA use at (908) 704-4600.	REVIEWS COMPLETED	Company of the Compan	
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